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(54) Title: **TRANSPORTERS AND ION CHANNELS**

(57) Abstract: The invention provides human transporters and ion channels (TRICH) and polynucleotides which identify and encode TRICH. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with aberrant expression of TRICH.

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and allogenic responses in pigs, validating the idea of channel blockers as safe and efficacious immunosuppressants (Cahalan, M.D. and K.G. Chandy (1997) Curr. Opin. Biotechnol. 8:749-756).

The discovery of new transporters and ion channels and the polynucleotides encoding them satisfies a need in the art by providing new compositions which are useful in the diagnosis, prevention, and treatment of transport, neurological, muscle, immunological, and cell proliferative disorders, and in the assessment of the effects of exogenous compounds on the expression of nucleic acid and amino acid sequences of transporters and ion channels.

SUMMARY OF THE INVENTION

The invention features purified polypeptides, transporters and ion channels, referred to collectively as "TRICH" and individually as "TRICH-1," "TRICH-2," "TRICH-3," "TRICH-4," "TRICH-5," "TRICH-6," "TRICH-7," "TRICH-8," "TRICH-9," "TRICH-10," "TRICH-11," "TRICH-12," "TRICH-13," "TRICH-14," "TRICH-15," "TRICH-16," "TRICH-17," "TRICH-18," "TRICH-19," "TRICH-20," "TRICH-21," "TRICH-22," "TRICH-23," "TRICH-24," "TRICH-25," "TRICH-26," and "TRICH-27." In one aspect, the invention provides an isolated polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-27, b) a naturally occurring polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-27, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-27, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-27. In one alternative, the invention provides an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:1-27.

The invention further provides an isolated polynucleotide encoding a polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-27, b) a naturally occurring polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-27, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-27, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-27. In one alternative, the polynucleotide encodes a polypeptide selected from the group consisting of SEQ ID NO:1-27. In another alternative, the polynucleotide is selected from the group consisting of SEQ ID NO:28-54.

Additionally, the invention provides a recombinant polynucleotide comprising a promoter

The invention also provides a method for screening a compound for effectiveness as an agonist of a polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-27, b) a naturally occurring polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence
5 selected from the group consisting of SEQ ID NO:1-27, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-27, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-27. The method comprises a) exposing a sample comprising the polypeptide to a compound, and b) detecting agonist activity in the sample. In one alternative, the
10 invention provides a composition comprising an agonist compound identified by the method and a pharmaceutically acceptable excipient. In another alternative, the invention provides a method of treating a disease or condition associated with decreased expression of functional TRICH, comprising administering to a patient in need of such treatment the composition.

Additionally, the invention provides a method for screening a compound for effectiveness as
15 an antagonist of a polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-27, b) a naturally occurring polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-27, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-27,
20 and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-27. The method comprises a) exposing a sample comprising the polypeptide to a compound, and b) detecting antagonist activity in the sample. In one alternative, the invention provides a composition comprising an antagonist compound identified by the method and a pharmaceutically acceptable excipient. In another alternative, the invention provides a method of
25 treating a disease or condition associated with overexpression of functional TRICH, comprising administering to a patient in need of such treatment the composition.

The invention further provides a method of screening for a compound that specifically binds to a polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-27, b) a naturally occurring polypeptide
30 comprising an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-27, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-27, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-27. The method comprises a) combining the polypeptide with at least one test compound

under suitable conditions, and b) detecting binding of the polypeptide to the test compound, thereby identifying a compound that specifically binds to the polypeptide.

The invention further provides a method of screening for a compound that modulates the activity of a polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-27, b) a naturally occurring polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-27, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-27, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-27. The method comprises a) combining the polypeptide with at least one test compound under conditions permissive for the activity of the polypeptide, b) assessing the activity of the polypeptide in the presence of the test compound, and c) comparing the activity of the polypeptide in the presence of the test compound with the activity of the polypeptide in the absence of the test compound, wherein a change in the activity of the polypeptide in the presence of the test compound is indicative of a compound that modulates the activity of the polypeptide.

The invention further provides a method for screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a sequence selected from the group consisting of SEQ ID NO:28-54, the method comprising a) exposing a sample comprising the target polynucleotide to a compound, and b) detecting altered expression of the target polynucleotide.

The invention further provides a method for assessing toxicity of a test compound, said method comprising a) treating a biological sample containing nucleic acids with the test compound; b) hybridizing the nucleic acids of the treated biological sample with a probe comprising at least 20 contiguous nucleotides of a polynucleotide selected from the group consisting of i) a polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:28-54, ii) a naturally occurring polynucleotide comprising a polynucleotide sequence at least 90% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:28-54, iii) a polynucleotide having a sequence complementary to i), iv) a polynucleotide complementary to the polynucleotide of ii), and v) an RNA equivalent of i)-iv). Hybridization occurs under conditions whereby a specific hybridization complex is formed between said probe and a target polynucleotide in the biological sample, said target polynucleotide selected from the group consisting of i) a polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:28-54, ii) a naturally occurring polynucleotide comprising a polynucleotide sequence at least 90% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:28-54, iii) a polynucleotide

Val Gly Ser Leu	Ile Tyr Glu Lys Leu	Gly Glu Lys Ala Phe Gly	110	115	120
Trp Pro Gly Lys	Ile Gly Ala Phe Val	Ser Ile Thr Met Gln Asn	125	130	135
Ile Gly Ala Met	Ser Ser Tyr Leu Phe	Ile Ile Lys Tyr Glu Leu	140	145	150
Pro Glu Val Ile	Arg Ala Phe Met Gly	Leu Glu Glu Thr Ser Arg	155	160	165
Glu Trp Tyr Leu	Asn Gly Asn Tyr Leu	Ile Ile Phe Val Ser Val	170	175	180
Gly Ile Ile Leu	Pro Leu Ser Leu Leu	Lys Asn Leu Gly Tyr Leu	185	190	195
Gly Tyr Thr Ser	Gly Phe Ser Leu Thr	Cys Met Val Phe Phe Val	200	205	210
Ser Val Val Ile	Tyr Lys Lys Phe Gln	Ile Pro Cys Pro Leu Pro	215	220	225
Glu Asn Gln Ala	Lys Gly Ser Leu His	Asp Ser Gly Val Glu Tyr	230	235	240
Glu Ala His Ser	Asp Asp Lys Cys Glu	Pro Lys Tyr Phe Val Phe	245	250	255
Asn Ser Gln Thr	Ala Tyr Ala Ile Pro	Ile Leu Val Phe Ala Phe	260	265	270
Val Cys His Pro	Glu Val Leu Pro Ile	Tyr Ser Glu Leu Lys Asp	275	280	285
Arg Ser Arg Arg	Lys Met Gln Thr Val	Ser Asn Ile Ser Ile Thr	290	295	300
Gly Met Leu Val	Met Tyr Leu Leu Ala	Ala Leu Phe Gly Tyr Leu	305	310	315
Thr Phe Tyr Gly	Arg Val Glu Asp Glu	Leu Leu His Ala Tyr Ser	320	325	330
Lys Val Tyr Thr	Leu Asp Ile Pro Leu	Leu Met Val Arg Leu Ala	335	340	345
Val Leu Val Ala	Val Thr Leu Thr Val	Pro Ile Val Leu Phe Pro	350	355	360
Val Arg Thr Ser	Val Ile Thr Leu Leu	Phe Pro Lys Arg Pro Phe	365	370	375
Ser Trp Ile Arg	His Phe Leu Ile Ala	Ala Val Leu Ile Ala Leu	380	385	390
Asn Asn Val Leu	Val Ile Leu Val Pro	Thr Ile Lys Tyr Ile Phe	395	400	405
Gly Phe Ile Gly	Ala Ser Ser Ala Thr	Met Leu Ile Phe Ile Leu	410	415	420
Pro Ala Val Phe	Tyr Leu Lys Leu Val	Lys Lys Glu Thr Phe Arg	425	430	435
Ser Pro Pro Glu	Leu Gln Ala Leu Ile	Phe Leu Val Val Gly Ile	440	445	450
Phe Phe Met Ile	Gly Ser Met Ala Leu	Ile Ile Ile Asp Trp Ile	455	460	465
Tyr Asp Pro Pro	Asn Ser Lys His His		470		

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Val Val Gly Arg	Val Phe Val Val Phe	Leu Val Val Ile Ser Ile			
	515	520			525
Leu Trp Ile Pro	Ile Ile Gln Ser Ser	Asn Ser Gly Gln Leu Phe			
	530	535			540
Asp Tyr Ile Gln	Ala Val Thr Ser Tyr	Leu Ala Pro Pro Ile Thr			
	545	550			555
Ala Leu Phe Leu	Leu Ala Ile Phe Cys	Lys Arg Val Thr Glu Pro			
	560	565			570
Gly Ala Phe Trp	Gly Leu Val Phe Gly	Leu Gly Val Gly Leu Leu			
	575	580			585
Arg Met Ile Leu	Glu Phe Ser Tyr Pro	Ala Pro Ala Cys Gly Glu			
	590	595			600
Val Asp Arg Arg	Pro Ala Val Leu Lys	Asp Phe His Tyr Leu Tyr			
	605	610			615
Phe Ala Ile Leu	Leu Cys Gly Leu Thr	Ala Ile Val Ile Val Ile			
	620	625			630
Leu Thr Arg Leu	Thr Trp Trp Thr Arg	Asn Cys Pro Leu Ser Glu			
	635	640			645
Leu Glu Lys Glu	Ala His Glu Ser Thr	Pro Glu Ile Ser Glu Arg			
	650	655			660
Pro Ala Gly Glu	Cys Pro Ala Gly Gly	Gly Ala Ala Glu Asn Ser			
	665	670			675
Ser Leu Gly Gln	Glu Gln Pro Glu Ala	Pro Ser Arg Ser Trp Gly			
	680	685			690
Lys Leu Leu Trp	Ser Trp Phe Cys Gly	Leu Ser Gly Thr Pro Glu			
	695	700			705
Gln Ala Leu Ser	Pro Ala Glu Lys Ala	Ala Leu Glu Gln Lys Leu			
	710	715			720
Thr Ser Ile Glu	Glu Glu Pro Leu Trp	Arg His Val Cys Asn Ile			
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Asn Ala Val Leu	Leu Leu Ala Ile Asn	Ile Phe Leu Trp Gly Tyr			
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Phe Ala					

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Ala Ile Gln Gly Gly	Leu Glu Trp Leu Lys	Gln Lys Val Phe Arg
	35	40
Leu Gly Glu Asp Trp	Tyr Phe Leu Met Thr	Leu Gly Val Leu Met
	50	55
Ala Leu Val Ser Tyr	Ala Met Asn Phe Ala	Ile Gly Cys Val Val
	65	70
Arg Gly Phe Ser Gln	Ser Ile Thr Pro Ser	Ser Gly Gly Ser Gly
	80	85
Ile Pro Glu Leu Lys	Thr Met Leu Ala Gly	Val Ile Leu Glu Asp
	95	100
Tyr Leu Asp Ile Lys	Asn Phe Gly Ala Lys	Val Val Gly Leu Ser

Ala Thr Lys Pro Gly Arg Ser Gly Lys Glu Ser Val Thr Glu Pro	20	25	30
Trp Ala Arg Val Pro Gly Ala Leu Gly Val Ala Ala Arg Gln Met	35	40	45
His Pro Lys Ser Ile Ile Thr Phe Arg Glu Ile Asn Gly Glu Tyr	50	55	60
Thr Gly Ala Val Asp Phe Pro Arg Leu Gly Val Arg Ala Ser Glu	65	70	75
Glu Thr Ala Leu Arg Glu Leu Lys Met Ser Lys Glu Leu Ala Ala	80	85	90
Met Gly Pro Gly Ala Ser Gly Asp Gly Val Arg Thr Glu Thr Ala	95	100	105
Pro His Ile Ala Leu Asp Ser Arg Val Gly Leu His Ala Tyr Asp	110	115	120
Ile Ser Val Val Val Ile Tyr Phe Val Phe Val Ile Ala Val Gly	125	130	135
Ile Trp Ser Ser Ile Arg Ala Ser Arg Gly Thr Ile Gly Gly Tyr	140	145	150
Phe Leu Ala Gly Arg Ser Met Ser Trp Trp Pro Ile Gly Ala Ser	155	160	165
Leu Met Ser Ser Asn Val Gly Ser Gly Leu Phe Ile Gly Leu Ala	170	175	180
Gly Thr Gly Ala Ala Gly Gly Leu Ala Val Gly Gly Phe Glu Trp	185	190	195
Asn Ala Thr Trp Leu Leu Leu Ala Leu Gly Trp Val Phe Val Pro	200	205	210
Val Tyr Ile Ala Ala Gly Val Val Thr Met Pro Gln Tyr Leu Lys	215	220	225
Lys Arg Phe Gly Gly Gln Arg Ile Gln Val Tyr Met Ser Val Leu	230	235	240
Ser Leu Ile Leu Tyr Ile Phe Thr Lys Ile Ser Thr Asp Ile Phe	245	250	255
Ser Gly Ala Leu Phe Ile Gln Met Ala Leu Gly Trp Asn Leu Tyr	260	265	270
Leu Ser Thr Gly Ile Leu Leu Val Val Thr Ala Val Tyr Thr Ile	275	280	285
Ala Gly Gly Leu Met Ala Val Ile Tyr Thr Asp Ala Leu Gln Thr	290	295	300
Val Ile Met Val Gly Gly Ala Leu Val Leu Met Phe Leu Gly Phe	305	310	315
Gln Asp Val Gly Trp Tyr Pro Gly Leu Glu Gln Arg Tyr Arg Gln	320	325	330
Ala Ile Pro Asn Val Thr Val Pro Asn Thr Thr Cys His Leu Pro	335	340	345
Arg Pro Asp Ala Phe His Ile Leu Arg Asp Pro Val Ser Gly Asp	350	355	360
Ile Pro Trp Pro Gly Leu Ile Phe Gly Leu Thr Val Leu Ala Thr	365	370	375
Trp Cys Trp Cys Thr Asp Gln Val Ile Val Gln Arg Ser Leu Ser	380	385	390
Ala Lys Ser Leu Ser His Ala Lys Gly Gly Ser Val Leu Gly Gly	395	400	405
Tyr Leu Lys Ile Leu Pro Met Phe Phe Ile Val Met Pro Gly Met	410	415	420
Ile Ser Arg Ala Leu Phe Pro Asp Glu Val Gly Cys Val Asp Pro	425	430	435
Asp Val Cys Gln Arg Ile Cys Gly Ala Arg Val Gly Cys Ser Asn	440	445	450
Ile Ala Tyr Pro Lys Leu Val Met Ala Leu Met Pro Val Gly Leu	455	460	465
Arg Gly Leu Met Ile Ala Val Ile Met Ala Ala Leu Met Ser Ser	470	475	480
Leu Thr Ser Ile Phe Asn Ser Ser Ser Thr Leu Phe Thr Ile Asp			